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I. The Electrical Response as an Index of Glandular Action

BY
W. B. CANNON AND McKEEN CATTELL

From the Laboratory of Physiology in the Harvard Medical School

Reprinted from The American Journal of Physiology,
Vol. XLI, No. 1, July, 1916

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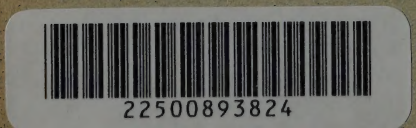

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STUDIES ON THE CONDITIONS OF ACTIVITY IN ENDOCRINE GLANDS

I. The Electrical Response as an Index of Glandular Action[1]

W. B. CANNON and McKEEN CATTELL

From the Laboratory of Physiology in the Harvard Medical School

Received for publication April 27, 1916

In the extensive literature of electrophysiology much has been reported concerning observed alterations of electrical potential in nerves and muscles under various circumstances, but relatively little attention has been given to the electromotive phenomena of glands. The studies of du Bois-Reymond, Rosenthal, Hermann, Luchsinger, Engelmann, and Biedermann on the cutaneous and other surface glands in the frog and fish and in the cat, dog, pig and goat indicated, more than thirty years ago, the possibilities of interesting research in this field. To some extent these possibilities have been realized in studies of the psychogalvanic reflex. The use of electrical methods for examining the glands of the interior of the body, however, has been almost wholly neglected. In 1885, Bayliss and Bradford (1) reported the results of an investigation of the electrical changes attending secretion by the salivary glands in the dog and cat, and a few years later Bradford (2) contributed further information on the same subject. In 1894, Bohlan (3) published a paper on the electrical effects produced by the gastric mucosa when stimulated through the vagus nerves. Any other papers dealing with electromotive phenomena of the glands that lie distant from the body surface, we have been unable to find.

An interest in the activities of the ductless glands, especially those without a secretion recognizable by present methods, led us to consider the possibility of applying to them the extremely delicate means now available for detecting slight electrical differences, with the hope that thereby further knowledge of their functions might be secured.

[1] The main results of this and the two following papers were presented before the American Physiological Society, December 29, 1915. See Proceedings, this journal, 1916, xl, p. 143.

Obviously an electrical change cannot yield information as to the nature of the materials elaborated in the several structures, it cannot determine the course which the products of secretion actually take in passing away from their region of origin, indeed it might leave somewhat uncertain whether secretion or preparation for secretion were the process occurring in a gland at any given period of disturbed potential. Nevertheless the method, by revealing the difference between relative quiet and activity, would indicate conditions which affect the functioning of glands and thus might suggest more definitive studies; it would show the quickness, the extent, and roughly the degree, of the response; and it might disclose significant new facts regarding relations which exist among the glands and which are mediated by the circulation. Despite its meager character such knowledge seemed worth seeking.

At the beginning of such a study of ductless glands there is obvious advantage in learning the capacities and limitations of the method as demonstrated in a gland which pours forth an easily recognizable secretion. For the purpose of preliminary tests we selected the submaxillary. And since we were, in the main, using cats in these researches we had the fortune of working on an animal in which both nerve supplies, the chorda and the sympathetic, evoke a considerable discharge of fluid. By use of the cat, therefore, it was possible to obtain insight into the electrical concomitants of a secretory activity which could be readily aroused from two different directions.

THE METHOD

The galvanometer used in these studies was of the d'Arsonval type.[2] Its sensitiveness is indicated by a deflection of 1 mm. on a scale 1 meter from the mirror when one volt is sent through 600 megohms. This sensitiveness, under the conditions of our observations, was sufficient for registering definite movements when physiological activity was induced in the glands, and yet was not so great as to make the instrument subject to minor adventitious alterations of potential.

The method of recording the galvanometer's deflection is shown by diagram in figure 1. On a firm wall-bracket, *T*, directly above the the scale, *S*, of the galvanometer, was placed a box painted black, inside and outside, and provided with a hinged cover, which when shut

[2] The instrument is that made by the Leeds and Northrup Company, Philadelphia, and listed as number 2220 in their catalogue.

admitted light only through a horizontal slit, *O*, about 1 mm. wide. This slit was 11.5 cm. above the top of the scale. Inside the box was the drum of a horizontal kymograph; and since the mechanism of the kymograph was outside the box the rate of revolution of the drum could be readily adjusted. When a record was to be made a sheet of sensitized paper was wrapped tightly around the drum and fastened with gummed paper, the drum was then set on the spindle of the kymograph and lowered into the box, and the box closed. All this process was carried on while the room was illuminated solely with ruby light. The light reflected from the mirror, *M*, to the slit in the box had its source in *E*, an electric bulb (6 volts, 21 candlepower) the filament of which was held vertical and permitted to send its rays out to the middle of the mirror through a narrow vertical opening. The rays reflected from the mirror were focussed on the sensitized paper[3] by means of a thin lens, *L*, placed near the galvanometer. The distance from the mirror to the paper was 45 cm. Obviously any motion of the mirror around the vertical axis of its support would result in a shift of the reflected beam of light along the horizontal slit, *O*.

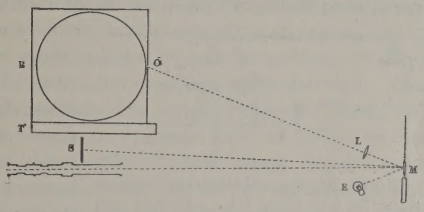

Fig. 1. Diagram of arrangement for observing and recording galvanometer deflections. For explanation, see text.

As indicated in figure 1, the arrangement allows the observer to watch the movement of the mirror through the telescope of the galvanometer at the same time that a record is being made.

A combined base line and time record was provided by a narrow beam of light directed on the slit, *O*, from another electric bulb. The electrical connections of this bulb are shown in diagram in figure 2. The current (at 8 volts) passing continuously through the filament of this bulb, *B*, was just sufficient to cause a slight glow which only dimly affected the sensitized paper. By means of another connection the dull glow of the filament was increased by an additional voltage, whenever a current was completed through the primary circuit of an inductorium *I*, by closure of the key, *M*. Thus the period of stimulation was registered on the revolving surface by a darkening of the dim

[3] The paper used was "standard" permanent bromide paper, quality B, made by the Eastman Kodak Company, Rochester, New York.

base line. A clock, making an electric contact every 30 seconds, momentarily magnetized the iron core, *C*, and thereby drew the spring, *S*, away from contact 1, and against contact 2 (these contacts were platinum). The stronger current thus sent for an instant through the filament produced a sharp flash which was registered as a black point on the base line. This registering of the half-minute intervals interfered only for a fraction of a second with any stimulation that might be in process.[4]

The non-polarizable electrodes used in contact with the tissues were similar to those described by Mines (4). Glass tubing, 8 cm. long and 5 mm. in internal diameter, was drawn to a point about 2 mm. in diameter. Into this pointed end was inserted a short length of soft cotton twine, which later afforded a gentle contact with the living tissue. The glass was then placed, point downward, in warm Ringer's solution containing 10 per cent gelatin. The fluid was deep enough to half fill the tubes. Six or eight such electrodes were thus prepared at one time. Usually this preparation was made in the afternoon for the next day. After standing over night in a cold room, the gelatin was so firm in the tubes that it supported in a thoroughly satisfactory manner the zinc sulphate poured in above it. When short zinc rods, soldered to copper wires[5] leading to the galvanometer, were placed in the zinc sulphate the electrodes were ready for use. These electrodes have each a resistance of approximately 1500 ohms. In the mass of gelatin in which they are set they can be kept for several days without deterioration, and removed as they are needed.

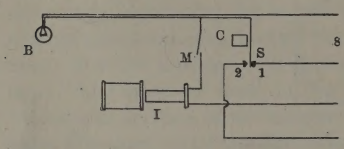

Fig. 2. Diagram of electrical connections for recording time intervals and duration of stimulation. For explanation see text.

Bayliss and Bradford, in their experiments on the submaxillary gland, set one leading-off electrode on the hilus of the gland and the other on the opposite surface. Apparently the object of this arrangement was to determine the difference of potential at the cell membranes lying between the duct and the lymph spaces. In our experience constant results have been obtained, however, with the gelatin electrodes situ-

[4] In developing the sensitive paper some sheets were darker than others. For uniform appearance the original photographs have been carefully copied in line drawings.

[5] The junction of the zinc and copper was covered with flexible wax.

ated one upon the gland being investigated, the other upon neighboring subcutaneous fascia[6] at a point near enough to other structures to be moistened with lymph. Secretion is then, except under conditions to be described later, accompanied by a negative relation of the gland to the indifferent surface, when these regions are connected through external conductors. Naturally the action current is occasioned only by such part of a circuit as is in fact active. And since stimulation of the chorda tympani, for example, makes active only the gland and not the surrounding structures, the current lines should be considered only with reference to the gland. The current lines would obviously be condensed under the electrode on the gland surface, but through the extensive area of contact between the gland and the tissues beneath it (which may be regarded as the other electrode) they would pass diffusely. In a complex gland like the submaxillary the highly confused relations of the cell membranes at which electrical differences would develop, and the simultaneity of action throughout the structure, would, in all probability, result in such antagonisms as to produce no effect whatever if only a sufficiently extensive region is taken for test. This suggestion is supported by the following experiment. We placed the two electrodes on outlying tissues on opposite sides of the gland and about 1 mm. distant from its border. Under these circumstances chorda stimulation failed to produce any action current that had an effect on the galvanometer; there appeared to be a nullification of the electrical differences in the secreting cells taken as a whole. An electrode placed at a point on the surface, however, should be regarded as having peculiar relations to the structures beneath. At that point doubtless there are cells facing ducts and backing on lymph spaces; and secretion by these cells would be accompanied by ionic alterations or by shifts of concentration, occurring at surfaces immediately below the electrode, which would definitely affect it. In other words, although a stimulated gland is simultaneously active in all parts, and consequently the attendant potential differences are likely to balance one another, still the electrical changes in a group of cells near the surface would be detected if one electrode is sharply localized in their neighborhood. These changes would produce current lines diverging from the electrode on the gland surface, passing widely-spread through the gland to surrounding tissues, and converging again to the electrode on the subcutaneous fascia. By this conception it has seemed to us possible to

[6] Subcutaneous fascia was selected as an indifferent tissue because of Waller's testimony to its inactivity.

account for the point on the gland surface being negative to the indifferent point on the skin. But whether this explanation is true or not, the fact remains.

One of the two wires connected with the zinc rods previously mentioned was marked with a black band. When the rod attached to this wire was placed in the gelatin electrode on the fascia, and the other rod was in the electrode touching the gland, a *negative* relation of the gland to the fascia through the external connections would cause the galvanometer to register on the sensitive paper an excursion *upward* (positive) from the base line. A *positive* relation was registered by a movement of the light beam in the opposite (*downward*, negative) direction.

As soon as the electrodes were in place on the tissues and connected with the galvanometer they invariably revealed a difference of potential between the two points of contact. This difference had to be compensated before the gland changes could be conveniently observed. In figure 3 is shown diagrammatically the arrangement of apparatus for compensation. The source of the opposed potential was a Daniell cell, *C*. Wires from the cell were connected with a pole changer, *P*, which permitted the direction of the current through the rheocord, *R*, to be reversed at will. A resistance box, *B*, interposed in the circuit, made readily possible any desirable adjustment in the resistance. And by means of the slide, *S*, which moved freely along the exposed wire of the rheocord, the demarcation current from the gelatin electrodes, *E* 1 and 2, could be precisely corrected.

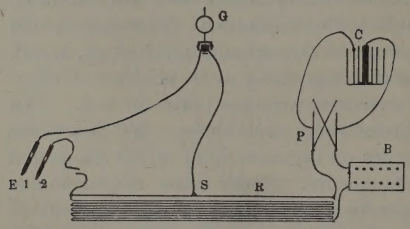

Fig. 3. Diagram of arrangement for connecting tissues with galvanometer, and for compensating the current of rest.

The presence of the compensating current, we found, became a source of error if the gelatin electrodes were both placed on the gland, or one on the gland and the other close by on adjoining tissue. Under these circumstances, after stimulation of the gland, by chorda impulses, for example, the galvanometer would indicate that the compensating current was prevailing; i.e., the galvanometer would move continuously outward in the direction which it would take if the compensating current were increased, or if the opposed current of rest were lessened.

An action current may or may not be demonstrated with both electrodes on the gland. When it is developed, it is probably due to a difference in the relations of the underlying active tissue to the two points of contact. If, with both electrodes on the gland, the action current has the same effect as the compensating current, the galvanometer moves out sharply in response to the glandular activity (action current), and instead of returning to zero, as normally, after the action current, it continues slowly outward. And if the action current is opposed to the compensation current, stimulation sends the galvanometer outward as usual and there is a prompt return to zero, but now the galvanometer continues to move slowly beyond zero, i.e., as if now controlled by the compensating current. This phenomenon can be accounted for by assuming conditions which lessen the current of rest (increased conductivity, increased permeability of membranes?). It does not occur when a sufficient amount of tissue *outside the active gland* intervenes between the electrodes. Then the factor of lessened potential of the current of rest is minimized by the inclusion in the circuit of considerable undisturbed tissue which offers a resistance little affected by changes in the gland, and the action current alone is manifested on excitation.

In certain cases there was a tendency for the galvanometer to move continuously in one direction even though compensation was repeatedly effected. Usually this phenomenon was more marked when the gland was first exposed than later. The reason for the phenomenon has not been determined; though probably one factor was a greater evaporation at one pole than at the other. When present it was a source of difficulty, for, dependent on the direction of the tendency to move, the return of the galvanometer to zero after an excursion was either incomplete or excessive.

In order that the galvanometer may give as true a record as possible of the electrical changes due to physiological processes it is necessary, of course, to keep the parts under and near the electrodes as quiet as possible. While working in the neck region we found that an L-shaped cannula inserted into the trachea, and clamped so that it held the structures in the larnygeal region in some tension, reduced to a minimum the influence of respiratory movements. Occasionally, exposed muscles in the field of operation will twitch. This trouble can usually be obviated by cutting across the muscles, or by severing their nerves. The various other ways in which motion at the contact between the electrode and the tissue was eliminated in different circumstances will be described later.

In some of the earlier experiments anæsthesia was dispensed with after the brain and the spinal cord (as far as the mid-thorax) had been pithed. Although such a preparation is quiet and is free from the influence of any depressive narcotic, the blood pressure is possibly too low for normal action. After some experience with urethane and ether, we came to the conclusion that etherization, if not too profound, was the best mode of rendering the animal motionless.

THE POSSIBLE FACTORS IN THE ELECTRICAL CHANGES IN GLANDS

Stimulation of the nerve connected with a gland may have at least two direct effects, one on the gland cells, the other on the smooth muscle of the blood vessels; and it may have at least two indirect effects, an alteration of the rate of blood flow through the vessels, and the motion of secreted fluid along ducts. Conceivably any of these variations might produce a change of potential. Evidently if vascular changes, vasoconstriction or vasodilation, were in themselves capable of giving rise to electrical differences, it would be difficult or impossible to draw conclusions regarding secretion in ductless glands having no demonstrable discharge. It is of prime importance, therefore, to determine what part any changes which are incidental to glandular activity itself may play in evoking electrical effects.

During the past five years evidence has appeared that contraction and relaxation of smooth muscle are accompanied by electromotive phenomena. The observations by Fuchs (6) on sipunculus and those of Brücke (7) on the retractor penis and of Arbeli and Brücke on the ureter have shown quite clearly that the electrical accompaniment of contraction is as characteristic of non-striate as it is of striate muscle. Still more pertinent was the observation by Straub (8), who noted, during the course of a study of the effects of certain conditions on the electrocardiogram, that the rise of blood pressure following asphyxia or a dose of adrenin was attended by a characteristic general shift of the galvanometer, which was recovered from as the pressure fell. He suggested that this phenomenon was a manifestation of the action current of the smooth muscle in the vessels. Although in Straub's experience local contraction of vessels, from exposure to cold, did not produce any electrical effect, and no shift was seen if the electrodes were on the same limb, the possibility of such an effect as a disturbing factor warrants careful consideration.

The question whether vasomotor changes might compound or modify

the electrical phenomena of glands was discussed and tested by Bayliss and Bradford, and later especially by Bradford (9). They made use of the effect of atropine in abolishing secretion without disturbing the action of nervous impulses on the smooth muscle of the blood vessels. After injecting atropine they found that when the chorda tympani failed to produce a salivary flow from the submaxillary gland there was simultaneously a disappearance of the electrical phenomena. Since atropine does not interfere with the vasodilation due to chorda influences the conclusion was justified that this vascular change was not a factor in the galvanometric response. Confirmation of Bayliss and Bradford's claim is seen in figure 4, which records electrical changes in the submaxillary gland on chorda stimulation (*a*), and on sympathetic stimulation (*b*), before the administration of atropine (1 cc. per kilo of a 1 per cent solution,injected intramuscularly between *b* and *c*); and the failure of the changes on chorda stimulation (*c*), five minutes after the injection, and on sympathetic stimulation (*d*) with the same weak current that was employed at first. When the current strength was increased sympathetic stimulation was again effective (at *e*), but no response could then be evoked through the chorda tympani.

There is the possibility that, although relaxation of smooth muscle in the vessels of a gland does not disturb the galvanometer, contraction might do so. Of course a shortening of the vascular muscle occurs during recovery from chorda dilation, and yet, as shown above (figure 4, *c*) no deviation of the galvanometer appears. The sympathetic influence on the vessels of the gland (in the dog) affords evidence, however which is more positive. Atropine in a sufficiently large dose not only inhibits the influence of the chorda tympani but also that of the sympathetic impulses. And Bradford found that when such a dose is given to a dog the abolition of the secretory effect of the sympathetic is coincident with the abolition of the electrical phenomena. Still other evidence that vasoconstriction alone, in the absence of secretion is not effective in producing electrical differences is found in the results of injecting pituitrin. As is well known, pituitrin causes a general rise of blood pressure by a direct constrictor action on the arterial walls. We have injected pituitrin[7] (0.2 cc.) into the femoral vein of a cat and raised the general blood pressure from 102 mm. of mercury to 158; there was, however, no secretion, and the galvanometer showed no electrical change whatever.

[7] We used the fluid preparation made by Parke, Davis and Company, Detroit.

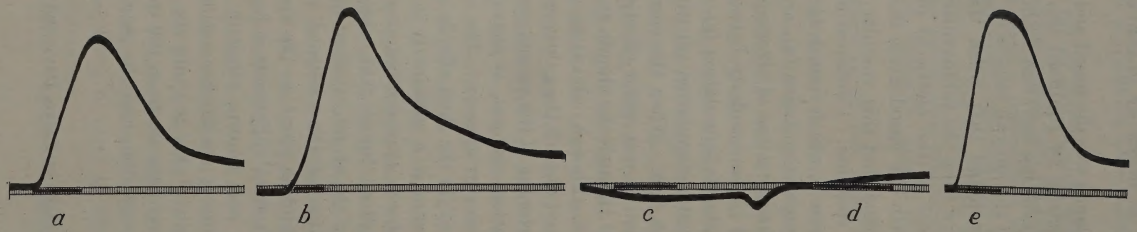

Fig. 4. Abolition of typical electrical response of submaxillary gland by atropine. Upper record, galvanometer; lower record, periods of stimulation; at *a* chorda stimulation 10 seconds, at *b* sympathetic stimulation 10 seconds, between *b* and *c* atropine 1 per cent, 1 cc. per k. injected intramuscularly, at *c* (5 minutes after the injection) chorda stimulation, at *d* sympathetic stimulation, at *e* sympathetic stimulation with much stronger current, which was ineffective when applied to the chorda. Time not recorded.

From these various experiments the conclusion seems well warranted that the electrical phenomena accompanying secretion are not due either to contraction or to relaxation of the smooth muscle in the vessels of the gland.

Another condition concomitant with vasomotor changes and also with external secretion is an altered rate of flow of fluid through capillaries and ducts. It has long been recognized that the movement of fluid through fine tubes is capable of causing differences of potential (10). May not the faster or slower blood flow and the progress of secreted material occasion the electrical phenomena?

Local vasodilation would be accompanied by a faster streaming, local vasoconstriction by a slower streaming through the capillaries. As already noted, both vasodilation and vasoconstriction will occur after atropine has stopped secretion of the submaxillary gland. But when secretion is lacking the electrical effect also is lacking. Under these circumstances, therefore, the altered rate of flow cannot have any influence in creating a difference of potential. We have tested the possibility further by raising blood pressure in the head through sudden occlusion of the aorta below the diaphragm and by suddenly lowering the pressure through compression of the heart. A pressure of 120 mm. of mercury was thus raised to 182 mm. and later lowered to 66 mm. Neither the faster flow from the high pressure nor the slower flow from the low pressure had any effect on the galvanometer. An altered rate of blood flow, we may conclude, is not a factor in producing the electrical change.

Although, in our experience, differences in the speed of streaming blood had no electrical effects, complete stoppage of the stream usually produced a deflection of the galvanometer which varied in extent and promptness of appearance. It seems probable, because of these variations, that the electrical changes are not consequent on the physical changes in the blood flow but are due rather to the influence of anemia on the gland cells.

Evidence indicates that the movement of secreted material along minute ducts of a gland likewise does not condition the electrical response. Bradford (11) noted, and we have confirmed him (see figure 5), that the galvanometer deflection starts before the saliva begins to move, and the maximum rate of the deflection is reached before the maximum rate of flow from the duct. Furthermore, when the escape of saliva is prevented by compressing the duct, repeated stimulations cause the usual electrical effect, though, as might be surmised from the

development of a back-pressure, the effect becomes gradually less (see figure 6, *b*, *c*, *d*). If now by removal of the compression the accumulated saliva is allowed to flow freely no potential difference appears (see figure 6 *e*).[8] This absence of an electrical change as secreted fluid begins to move or ceases to move along ducts is in accord with the conclusion reached in the previous paragraphs that the physical changes in the blood flow—starting, stopping, or going faster or slower—are not the occasion for electromotive phenomena.[9]

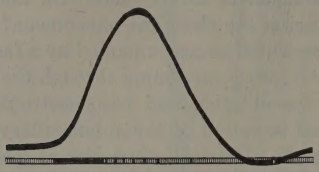

Fig. 5. Electrical change starting before saliva begins to move. Upper record, galvanometer. Lower record, dark band, chorda stimulation, 10 seconds; vertical lines, drops of saliva, except first one which marks moment when saliva began to flow in cannula. Last drop, white line on curve. Time not recorded.

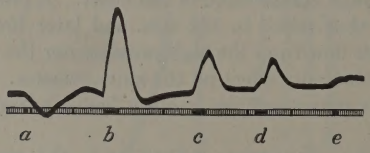

Fig. 6. Action currents of submaxillary gland after duct closed. Upper record, galvanometer. Lower record, time in half-minutes; at *a* clip on duct (manipulation); at *b*, *c*, and *d*, chorda stimulation, 10 seconds; at *e* clip removed (manipulation).

An action current will accompany secretion after the blood supply has been removed. Figure 7 records the electrical changes occurring in the right submaxillary gland. At *a* the right common carotid artery was clamped (the left had been clamped previously). About one minute later (at *b*) the cervical sympathetic was stimulated for ten seconds. The usual electrical change occurred attended by secretion.

[8] It was impossible to avoid slight electrical changes due to manipulation while the clip was being applied and removed (at *a* and *e*).

[9] In this discussion the reservation is made that a more sensitive galvanometer might reveal electrical differences not shown by the instrument used by us.

At *c* the clamp was removed from the right carotid. The record of electrical change differs from the normal chiefly in the absence of a rapid return to the base line (cf. figures 5 and 6), but the upward curve is characteristic and adds further to the proof that the electrical response does not arise from vascular changes. Favorable to that conclusion, also, is Bohlan's observation that vagus stimulation calls forth an action current of the gastric mucosa even though the aorta is clamped.

Other reasons for concluding that the functional activity of the secreting cells, and not muscular contraction or movement of fluid through fine tubules, determines the appearance of an action current in glands, will be noted in later papers. Thus the latent period of the action current in the thyroid gland differs from that of the adrenal, and in both these glands the period is much longer than in the submaxillary. Also the duration of the action current differs markedly in different glands; in the submaxillary it may last not more than a half-minute, in the thyroid and adrenal it commonly lasts much longer, as a result of brief electrical stimulation of nerves. There is no reason for supposing that the smooth muscle in the blood vessels of these glands varies either in the quickness of its response or in the persistence of its altered state (contraction or relaxation). The variations in the character of the action currents, typical of the several glands, contribute strongly to the argument that the electrical changes are reliable manifestations of a functional response.

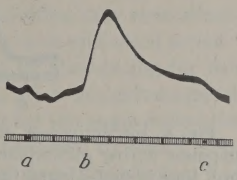

Fig. 7. Action current of submaxillary gland after carotid arteries closed. Upper record, galvanometer, connected with right submaxillary gland. Lower record, time in half-minutes; at *a* right carotid closed (left closed previously), at *b* sympathetic stimulated 10 seconds, at *c* clip removed from right carotid.

SUMMATION PHENOMENA

As illustrating the possibility of using the electrical method to obtain insight into the conditions of activity of glands the results of combined chemical and nervous stimulation may be cited. Figure 8 shows the usual effect of nervous influences after pilocarpine. At *a* 1 cc. of pilocarpine (1:1000) was injected into the femoral vein. A persistent secretion soon started, accompanied by a persistent positive electrical change. At *b* the chorda tympani was stimulated for 15 seconds, but

without effect. About 30 seconds later (at *c*) stimulation of the cervical sympathetic trunk sent the galvanometer deflection from +40 to +35, then out to +42, and slowly back to +25.[10] In this instance the excitation induced by pilocarpine was such that the chorda influences, which pilocarpine is supposed to mimic, no longer had any effect. The sympathetic influences, however, were still capable of increasing the activity of the gland.

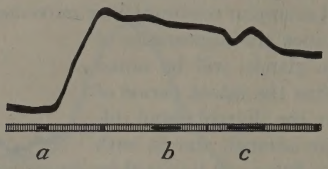

Fig. 8. Ineffectiveness of chorda impulses and effectiveness of sympathetic impulses during pilocarpine action. Upper record, galvanometer. Lower record, time in half-minutes; at *a* 1 cc. pilocarpine (1: 1000) injected intravenously, at *b* chorda stimulation, at *c* sympathetic stimulation (see text).

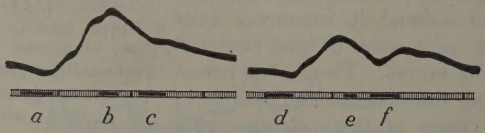

Fig. 9. Effectiveness of chorda impulses and ineffectiveness of sympathetic impulses during adrenalin action. Upper record, galvanometer. Lower record time in half-minutes; at *a* 1 cc. adrenalin (1: 10,000) injected intravenously, at *b* chorda stimulation, at *c* sympathetic stimulation, at *d* another adrenalin injection (1 cc., 1: 10,000), at *e* sympathetic stimulation, at *f* chorda stimulation.

The conditions of excitation in the submaxillary are quite different when adrenin is administered. In the cat this substance calls forth a secretion of watery saliva and an attendant electrical effect. In figure 9 is shown the record of the galvanometer after 1 cc. of adrenalin (1: 10,000) was injected (at *a*) intravenously. When the effect was maximal, the chorda tympani nerve was stimulated (at *b*), and the movement in the positive direction was definitely increased; at *d* an-

[10] The plus sign (+) indicates a movement of the galvanometer so that record *above* the base line is registered, i.e., the gland is negative to the fascia (see p. 44). The numbers refer to millimeter divisions on the galvanometer scale.

other injection of adrenalin was made, and near the summit of the curve stimulation of the sympathetic was without influence, but when on the return the chorda was stimulated a considerable increase of the positive deflection was registered (from +5 to +12). In another instance, after sympathetic impulses had been proved impotent during the acme of adrenalin action, a second dose of adrenalin caused an excursion to +26; and when at this maximum, chorda stimulation for 10 seconds increased it to +41. In these instances excitation of certain glandular components by adrenin made ineffective the sympathetic impulses which this substance simulates; but other components subject to chorda influences were not involved, and when they were stimulated, the gland, as the galvanometer shows, became still more active.

Confirmation of these results was obtained by stimulating for five seconds, first the chorda tympani, and then, after the galvanometer had moved to a maximum of +22, stimulating for the same period the sympathetic trunk. The excursion was thus increased to +32. Conversely, when sympathetic stimulation preceded and the deflection had reached +20, excitation of the chorda fibres increased it to +42.

REVERSAL OF THE SIGN OF THE RESPONSE

A phenomenon which has been repeatedly noted in electrical studies of glandular action is reversal of the response. Thus Engelmann (12) reported that the usual effect of stimulating the nerve of a piece of frog's skin is a negative variation of the normal "in-going" (i.e., external surface negative to internal through the galvanometer) current of the skin. In Hermann's observations (13), on the other hand, the commonest effect was a positive variation—an increase—of the normal current. Bayliss and Bradford (14), although admitting that it is "scarcely possible to speak of a normal excitatory variation," found, by making examinations throughout the year, that most of the time they confirmed Hermann but during the breeding season (February and March) they saw what Engelmann had seen. According to Waller (15) the reversal of response may occur within a few minutes—the first effect of stimulation is in the Engelmann sense, the second, five minutes later, is less so, and the third, five minutes later still, is in the direction Hermann described.

We have had similar experiences in recording the action currents of internal glands. For example in one animal the thyroid gland when stimulated will be negative in relation to the indifferent skin, in an-

other it will show regularly a positive relation.[11] This is admittedly disturbing. Various suggestions come to mind as possibly accounting for it, such as the position of the electrode on the gland, the degree of pressure, a reversal of activity, the lessening of an activity already existent rather than its increase on stimulation, or so much greater permeability that the compensating current prevails. Many of these suggestions were ruled out by a result which we obtained in some animals on stimulating either the chorda tympani or the cervical sympathetic trunk after the submaxillary gland was set in prolonged secretion by pilocarpine (1 cc. 1:1000, intravenously). Under these circumstances the nerve impulses, instead of causing the gland to become increasingly negative to the skin, rendered it less negative (see figure 10, *c*, *d* and *e*). And when the potential accompanying the secretory activity was compensated, sympathetic or chorda stimulation (figure 10 *f*) instead of making the gland negative to the skin (as figure 10, *a*) now made it positive. Later the nerve impulses caused a primary slight movement of the galvanometer in the "normal" direction, but there followed at once a much more extensive excursion opposed to that. In these experiments there was no shift in the position of the electrode nor any variation of its pressure on the gland. As a result of the stimulation there was the normal effect of chorda impulses—a marked increase in the rate of secretion. Lessening of the physiological process or reversal of it cannot, therefore, be invoked to account for the phenomenon.

For the present the reversal of the sign of the response remains unexplained. It may belong in the same category with numerous other instances of exactly opposed effects of the same stimulus, dependent on the state of the responding tissue (16). From the evidence here given, however, we may rest assured that the electrical change, either positive or negative, which follows stimulation is an indication of glandular activity. Like other indicators of fundamental physiological processes the electrical change develops gradually to a maximum and more gradually subsides again, and it follows after a definite latent period. As Waller has remarked, the obvious delay between excitation and response is "a sure and reassuring sign that we are dealing with a true physiological response, outside all possibility of coarse physical fallacy."

It is obvious that many more aspects of the functioning of the submaxillary gland are capable of investigation by the electrical method.

[11] The terms "negative" and "positive" we employ with the understanding that they refer to two regions as related through external connections.

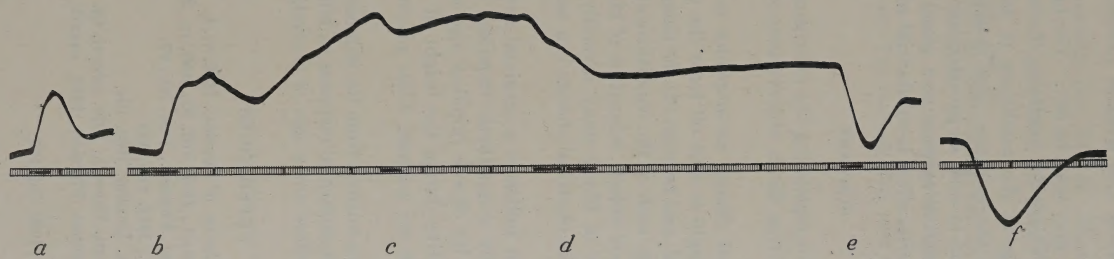

Fig. 10. Reversal of electrical response during pilocarpine effects. Upper record, galvanometer. Lower record, time in half-minutes; at *a* chorda stimulation, at *b* 1 cc. pilocarpine (1: 1000) injected, at *c* sympathetic stimulation, at *d* sympathetic stimulation again, at *e* chorda stimulation (with return to zero), at *f* chorda stimulation again after compensation. Secretion continued during the whole period after *b*, and was increased during the nerve stimulations.

For the present, however, they may be left. The brief study here recorded was of value to us chiefly for justifying the method as a means of getting more knowledge of the conditions of activity of ductless glands. We believe that the evidence here presented warrants the employment of this method in such an investigation and that when a difference of electrical potential appears in a gland as a result of an altered condition the electrical effect is substantial witness to secretory activity.

SUMMARY

A method is described for registering the excursions of a d'Arsonval galvanometer while permitting direct observations of the deflection on the scale.

Because (1) an electrical change accompanies secretion of saliva, even though the blood supply is shut off from the gland, or the flow through the duct is stopped; and because (2) the change is absent when secretion is absent although each of the conditions attendant on secretion—as contraction of blood vessels, relaxation of blood vessels, faster flow of blood, slower flow of blood—may severally be induced, the conclusion is drawn that the electrical change is a manifestation solely of the secretory process.

When the action current indicates a maximal activity of the submaxillary gland, excited by sympathetic impulses, the electrical response can be augmented by chorda impulses and *vice versa;* sympathetic impulses are ineffective during the height of an adrenin effect and chorda impulses cause no increase while pilocarpine is strongly operative.

The direction of the action current from the submaxillary gland may be reversed although the physiological response to stimulation remains as usual. Reversal is therefore not a sign of a reversed process in the gland.

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